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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,185	DENISE ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-23 and 26-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20060914*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/28/04;12/6/04;2/28/05;7/27/06.

1. Applicant's election with traverse of marker MMT07944 as set forth in SEQ ID NO: 20614, the extension primer set forth in SEQ ID NO: 23124, and a single pair of primers wherein each primer has the sequence of nucleotides 275-350 of SEQ ID NO: 20614, wherein the nucleotide corresponding to position 300 can be a "g" or an "a," as well as amendments to claims 1-26 and the addition of claims 27-32 in the reply filed on 11/20/2006 is acknowledged. The traversal is on the ground(s) that search burden alone is insufficient grounds for restriction and the SNPs of the present invention are not independent and distinct. This is not found persuasive because first, there is a serious search burden on the examiner to examine the claims as written, and furthermore, as amended. For example, claim 1 as amended, recites a series of at least ten polynucleotides consisting of a fragment of at least 20 contiguous nucleotides of a bovine genome or a complement thereof, wherein each polynucleotide comprises a SNP associated with a trait that is about 500,000 or less nucleotides from position 300 of any one of SEQ ID Nos: 19473 to 21982, wherein each of the isolated polynucleotides is less than or equal to about 500,000 nucleotides in length. The claim encompasses not only every single SNP possible for a span of 1,000,000 nucleotides surrounding position 300 of any one of the 2,510 sequences listed, but it does not even indicate a particular SNP (i.e. "g" to "a") for each location of each isolated polynucleotide within the sequence length of 20 to 500,000 nucleotides. The claim therefore encompasses the possibility of billions of sequences within the series and would definitely be a serious search burden on the examiner and the resources of the Office.

Second, the SNPs of the instant invention are independent and distinct. Election of one particular SNP is not an election of species. If it were so, the genus of polymorphisms represents every possible variation which could occur at about 500,000 or less nucleotides from position 300 of any one of SEQ ID Nos: 19473 to 21982, including a plethora polymorphisms within and outside the range of the indicated sequences. Also, a claim which states a series of isolated polynucleotides, each comprising any SNP about 500,000 or less nucleotides from position 300 of any one of SEQ ID Nos: 19473 to 21982, and does not even describe each particular SNP for any of the isolated polynucleotides, comprises "species" that are not representative in any way of each other, or of the genus.

Applicants further argued that groups of SNPs are similarly connected in design, operation, and effect. Although one SNP might be associated with a similar trait as another SNP, they are in no means connected to each other in design, operation and effect. For example, a G to A change at position 33 shares no structural relationship with the G to A change at position 57 because each of these changes occurs in distinct sequence regions, with distinct effects and with no necessary relationship. So there is no common structure between polymorphisms.

Applicants stated the SNPs of claims 1-26 (as amended) and new claims 27-32 are not only capable of use together, they must be used together for trait mapping and in most applications of trait interference (page 14), however applicants have failed to indicate which SNPs would be useful in use together for a particular trait. This was also discussed in a phone interview with the applicants on August 31, 2006 following the

restriction requirement to one particular SNP, where applicants stated a combination could be used in tracking meat of a bovine subject. Each sequence comprising a specific SNP within the combination might be useful for characterizing different traits of the meat of the bovine subject. With that said, as the examiner stated in the phone interview, applicants also have the option of amending the claims to a combination of defined sequences, each comprising a particular SNP (see attached interview summary). It is acknowledged that the applicants have amended the claims 1-26 to reflect a combination of polynucleotides, however, the applicants have not defined a specific combination of sequences, each comprising a particular SNP. The MPEP states that applications containing only composition claims reciting different combinations of individual nucleotide sequences, such as set forth in example (C) (a combination of DNA fragments, said combination containing at least thirty different DNA fragments selected from SEQ ID Nos. 1-1,000), will be subject to a restriction requirement. Applicants will be required to select one combination for examination. If the selected combination contains ten or fewer sequences, all of the sequences of the combination will be searched. If the selected combination contains more than ten sequences, the combination will be examined following the procedures set forth above for example (B). More specifically, the combination will be searched until one nucleotide sequence is found to be allowable with the examiner choosing the order of search to maximize the identification of an allowable sequence. The identification of any allowable sequence(s) will cause all combinations containing the allowed sequence(s) to be allowed (MPEP 803.04).

Additionally, the examiner stated that the restriction election was to one of the options, being either the original restriction requirement of *one* particular SNP, and *one* primer pair, and *one* probe associated with the SNP; or a specific combination of sequences comprising particular SNPs. The applicants also failed to elect one option since they have amended the claims to reflect both a combination of polynucleotides comprising a SNP, and combinations of primer pairs and probes for a particular SNP.

Since the applicants have failed to indicate a defined combination to examine, and amend the claims to one of the restriction options, for purposes of examination, only the claims encompassing elected SNP marker MMT07944, corresponding to position 300 of SEQ ID NO: 20614 being a "g" or an "a" will be examined.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24-25 are under examination for the elected SNP marker MMT07944, corresponding to position 300 of SEQ ID NO: 20614 being a "g" or an "a."

3. Claims 1-20, 21-23, 26-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/20/2006.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 24-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 24-25 encompass an isolated polynucleotide comprising (a) a polynucleotide that is at least 20 nucleotides in length and is at least 90% identical to a fragment of at least 20 contiguous nucleotides of a bovine genome; (b) or a complement (a), wherein the fragment is at least 20 contiguous nucleotides of the bovine genome comprises a nucleotide occurrence of a single nucleotide polymorphism that corresponds to position 300 of SEQ ID NO: 20614, being a "g" or an "a."

The claims thus encompass sequences that are at least 90% identical to the sequence recited. Since SEQ ID NO: 20614 consists of 600 nucleotides, a sequence with 90% identity would have as many as 60 variant nucleotides. These 60 variant nucleotides can be in any position and combination thus resulting in an enormous number of nucleotide sequences when all combination of positions is considered.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches SEQ ID NO: 20614. The specification does not teach any sequences that are 90% identical to the SEQ ID NO recited or any homologous sequences.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides the structural limitation the sequences are of position 300 of each SEQ ID: 19473 to 21982 comprising a SNP, but such SNPs are by no means connected to each other in design, operation and effect and there is no common structure between any of the polymorphisms. The claims encompass any nucleic acid molecule that has at least 90% sequence identity to at least 20 contiguous nucleotides comprising position 300 of SEQ ID NO:20614. Further the use of primers targeting the isolated polynucleotide with at least 90% identity would not only allow detection of bovine, but of other organisms. This is an enormous genus of nucleotide, because the specification does not teach homologous sequences, or identical sequences other than SEQ ID NO: 20614 in the sequence listing.

In the instant application, the provided information regarding nucleic acid SEQ ID NO: 20614, does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of an isolated polynucleotide. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding SEQ ID NO: 20614 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 112 – Enablement

Claims 24-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to one polymorphism at position 300 of SEQ ID NO: 20614, wherein such a polymorphism associated with the trait of bovine meat tenderness (Tables 1A and 1B). The invention is in the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass an isolated polynucleotide that is between 20 to 600 nucleotides in length and at least 90% identical to a fragment of at least 20 contiguous nucleotides of a bovine genome, or a complement thereof, wherein the polynucleotide comprises a SNP at position 300 of SEQ ID NO: 20614, but a sequence with 90% identity would have as many as 60 variant nucleotides in any position and combination.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as bovine meat tenderness. Screening each possible polymorphism in the bovine genome represents an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

Even the art associated with identifying bovine SNP markers for trait characterization, demonstrates the unpredictability of polymorphism association. Heaton et al. ("Selection and use of SNP markers for animal identification and paternity analysis in U.S. beef cattle," Mammalian Genome, 2002, Vol.13, pp.272-281) state that SNP markers and can be used for association mapping to identify chromosomal regions containing loci involved with phenotypic traits and has been advocated as a method for mapping, however, a significant problem is the potential for spurious associations (i.e. false positives) that arise from unrecognized population stratification or recent admixture (page 279, 2nd column, 2nd paragraph). Heaton also states that at least 34 SNPs would be required to identify all 270,000 cattle registered by the American Angus Association,

40 SNPs for all of the 100 million cattle in the U.S., and 43 SNPs would be required for all of the 10 million cattle ever registered by the American Angus Association.

Therefore, it is highly unpredictable whether some currently unknown polymorphism in the bovine genome would have any association with any phenotype. Furthermore, one SNP cannot be used solely to identify a particular phenotype or genotype.

Working Examples

The specification has working examples where in Tables 2-4 represent disequilibrium analysis in relation to SNP distance from three different SNPs. In Table 2, SNPs MMBT13976, MMBT09532, and MMBT09533 are shown to be within 500,000 nucleotides of SNP marker MMBT22302 and all show significant association to average daily gain. There is no data corresponding to their significance levels for association of the particular trait, there are only 4-5 SNPs stated to be correlated with such a trait – there is no reference to where these sequences correspond to the bovine genome in order to determine the distance and position of each sequence and corresponding SNP to each other. The sequences are related to particular "contigs" wherein the specification does not indicate where in the bovine genome such contigs are located and where they are located in respect to each other, and the particular SNPs listed in Tables 1A and 1B. Furthermore, Table 1B states that MMBT13976 is also associated with tenderness, retail yield and fat thickness, and it does not show the significance data for each trait in relation to the polymorphism. MMBT09532, and MMBT09533 are also

show to be associated with other traits as well, not only average daily gain. Tables 3 and 4 also show similar patterns for each associated polymorphism.

Guidance in the Specification.

The specification does not provide sufficient evidence to demonstrate the association of any polymorphism being associated with a particular trait, nor does it provide any significant linkage equilibrium data for the polymorphisms for mapping. The specification shows a total of 2,510 polymorphisms associated with one or more traits, however it does not provide any statistical data which shows their significance to such traits, or to each other for mapping. The specification only states that SNP occurrences listed in Tables 1A and 1B as associated with a "high" trait characteristic are likely to be associated with a value greater than 50th percentile of the bovine population for the relevant trait, and those with a "low" trait are likely to be associated with a value less than 50th percentile of the bovine population for the relevant trait (page 21, [0060]), therefore, a SNP associated with 49% of a bovine population for a particular trait is deemed a low trait characteristic SNP, but a SNP associated with 51% of a bovine population for a different trait is deemed a high trait characteristic SNP. The applicant's elected polymorphism; MMBT07944, i.e. position 300 (g/a) on SEQ ID NO: 20614 has no significance data for it's relationship to tenderness in Tables 1A or 1B. In Table 1B, it states that MMBT07944 is sequences 742-1341 of contig 19866881037958, however there are no other sequences in Table 1B shown to be a "nearby sequence" of this contig and other sequences nearby that SNP do not necessarily associate with the same trait. For example, other polymorphisms also associated with meat tenderness in Tables 1A and 1B, such as MMBT02858, MMBT16580, MMBT21179, MMBT05003, MMBT18802, MMBT18799, and MMBT18797, are not a "nearby sequence" to

MMBT07944. Therefore such a polymorphism could not be used for trait mapping of the instant invention.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching gene association studies are highly unpredictable is demonstrated by Heaton, Lucentini, Wacholder and Ioannidis. The specification provides one with no written description or guidance that leads one to a reliable method where any polymorphism will be associated with a particular trait, or could be used together for trait mapping. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms for phenotype identification and trait mapping as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of working examples which do not address the full scope of the claims at issue and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicants elected SNP of position 300 of SEQ ID NO: 20614, an extension primer set forth in SEQ ID NO: 23124, and a single pair of primers wherein each primer has the sequence of nucleotides 275-350 of SEQ ID NO: 20614, and for the first primer, the terminal nucleotide in this position is a "g" and for the second primer, the terminal nucleotide in this position is an "a." The election of the primer pairs is confusing because it is unclear what is meant by "terminal nucleotide." If the primer ends at position 300 (i.e. terminal nucleotide), then it would not correlate with the election of a primer having the sequence of nucleotides 275-350 of SEQ ID NO: 20614. If the primer comprises position 300 being a "g" or an "a," then it would correlate with the election of a primer having the sequence of nucleotides 275-350 of SEQ ID NO: 20614, however, it would be unclear what is meant by "terminal nucleotide." For the purposes of examination, the search will be done for the primer pairs having the sequence of nucleotides 275-350 of SEQ ID NO: 20614, wherein the first primer has a "g" at position 300, and the second primer has position "a" at position 300 of the sequence. Furthermore, the election of "an extension primer" is confusing because it is unclear whether this is another primer election as meant for polymerase extension, or it is for the sole use of hybridization as meant for a probe. For the purposes of examination, it will be treated as a probe since this was the original restriction requirement.

SUMMARY

8. Claims 24-25 are free of the prior art, but are rejected for other reasons. No art has been found teaching or suggesting an isolated polynucleotide, at least 90% identical to a fragment of at least 20 contiguous nucleotides of a bovine genome, or a complement thereof, wherein the polynucleotide comprises a SNP at position 300 of SEQ ID NO: 20614. No art has been found teaching or suggesting a primers having the sequence of nucleotides 275-350 of SEQ ID NO: 20614, wherein position 300 in the first primer is a "g" and position 300 of the second primer is an "a." No art has been found teaching the probe having the sequence of SEQ ID NO: 23124.

CONCLUSIONS

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 2/4/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

2/5/07